Olmesartan vs ramipril in the treatment of hypertension and associated clinical conditions in the elderly: a reanalysis of two large double-blind, randomized studies at the light of the most recent blood pressure targets recommended by guidelines

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Abstract: In this paper, we present the results of a reanalysis of the data of two large randomized, double-blind, parallel group studies with a similar design, comparing the efficacy of an angiotensin-receptor blocker (olmesartan medoxomil) with that of an angiotensin-converting enzyme inhibitor (ramipril), by applying two different blood pressure targets recently recommended by hypertension guidelines for all patients, irrespective of the presence of diabetes (<140/90 mmHg), and for elderly hypertensive patients (<150/90 mmHg). The efficacy of olmesartan was not negatively affected by age, sex, hypertension type, diabetes status or other concomitant clinical conditions, or cardiovascular risk factors. In most cases, olmesartan provided better blood pressure control than ramipril. Olmesartan was significantly more effective than ramipril in male patients, in younger patients (aged 65–69 years), in those with metabolic syndrome, obesity, dyslipidemia, preserved renal function, diastolic hypertension, and, in general, in patients with a high or very high cardiovascular risk. Interestingly, patients previously untreated or treated with two or more antihypertensive drugs showed a significantly larger response with olmesartan than with ramipril. Thus, our results confirm the good efficacy of olmesartan in elderly hypertensives even when new blood pressure targets for antihypertensive treatment are considered. Such results may be relevant for the clinical practice, providing some hint on the possible different response of elderly hypertensive patients to two different drugs acting on the renin–angiotensin system, when patients are targeted according to the blood pressure levels recommended by recent hypertension guidelines.

Keywords: arterial hypertension, elderly, guidelines, olmesartan medoxomil, ramipril

Introduction

Until recently, major guidelines recommended two distinct blood pressure targets for treated hypertensives, namely <140/90 mmHg in low-moderate risk individuals and <130/80 mmHg in high-risk ones.1,2 According to these guidelines, the blood pressure goal in treated older patients had to be the same as in younger patients, namely <140/90 mmHg or below, if tolerated.1,2 However, such recommendations were not supported by incontrovertible trial evidence. As a matter of fact, in all the large randomized trials of antihypertensive treatment in the elderly, showing a reduction in
cardiovascular events through lowering blood pressure, the average systolic and diastolic blood pressure levels attained with treatment were never <140/90 mmHg.\textsuperscript{3,4} Other trials of more vs less intensive blood pressure lowering were unable to demonstrate benefits, in either aged individuals or high-risk hypertensive patients, by lowering systolic blood pressure <140 mmHg.\textsuperscript{5–12} Additionally, the results of extensive reviews of randomized controlled trials showed that recommendation to lower blood pressure <130/80 mmHg in patients with diabetes or a history of cardiovascular or renal disease was not supported by any evidence.\textsuperscript{3,12–14}

Taken together, results of all these studies suggested that evidence-based recommendations could be a most appropriate and modern approach to hypertension treatment management. Accordingly, most recent guidelines now recommend that patients with arterial hypertension associated with diabetes or chronic kidney disease must be treated to attain the goal of systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg. They also suggest that in older persons it may be sufficient to treat high blood pressure to a target of 150/90 mmHg or lower.\textsuperscript{1,2,14–17}

Given these premises, the question arises as whether the current available antihypertensive armamentarium, and particularly monotherapies, may be suitable to achieve modern blood pressure targets in older individuals, regardless of the presence of associated clinical conditions or additional cardiovascular risk factors. The availability of a large database of elderly hypertensive patients enrolled in two randomized, double-blind, parallel group studies with a similar design, comparing the efficacy of an angiotensin-receptor blocker (ARB), olmesartan medoxomil, with that of the angiotensin-converting enzyme (ACE)-inhibitor, ramipril, gave us the possibility to explore such a scenario.\textsuperscript{18,19} The original studies were devised at the time when old recommendations were still valid, and thus blood pressure targets differed between nondiabetics (<140/90 mmHg) and diabetics (<130/80 mmHg). Therefore, in the present paper we reanalyzed the data and compared the results by applying two different blood pressure targets indicated by the new hypertension guidelines: <140/90 mmHg, irrespective of the presence of diabetes, and <150/90 mmHg, as recommended for older hypertensives.

**Methodology**

The details on the study design and population can be found in previous publications.\textsuperscript{18–20} Briefly, the two original studies\textsuperscript{18,19} had a multicenter, randomized, double-blind, parallel group design, consisting of a 2-week washout with placebo, followed by 12 weeks of treatment with olmesartan medoxomil or ramipril at initial doses of 10 or 2.5 mg once daily, respectively. The initial drug dose could be doubled after the 2nd or 6th week of treatment in case of lack of normalization (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg for non-diabetic, systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg for diabetic patients). Elderly patients aged between 65 and 89 years, of either sex, with grade 1 or 2 essential hypertension (systolic blood pressure between 140 and 179 mmHg and diastolic blood pressure between 90 and 109 mmHg) were studied.

All patients gave their written informed consent before being enrolled in the study. The study was approved by the Ethics Committees of each study center. As in the original studies, analysis was performed on patients who were eligible for intention-to-treat, defined as all randomized patients receiving at least one dose of active treatment drug and having at least one office blood pressure measurement after randomization, using the last-observation-carried-forward method for patients prematurely leaving the study.

Response to antihypertensive treatment was evaluated by using a blood pressure target of <140/90 mmHg in all patients, irrespective of the presence of diabetes, and <150/90 mmHg, as recommended for older hypertensives. Analysis of variance was used to assess the differences between groups for continuous variables, whereas comparison of normalized patients was performed by the chi-squared test. Subgroup analyses for sex, age groups, level of cardiovascular risk, type of hypertension, metabolic status, renal functions status, number and type of previous antihypertensive drugs, and according to drug tolerability were also made. The level of statistical significance was kept at 0.05 throughout the whole study. Data are shown as means ± standard deviation (SD) or as numbers and percentages.

**Results**

**Treatment efficacy according to new blood pressure targets in the whole study group**

The pooled dataset from the two studies consisted of 1,426 patients (intention-to-treat population) of which 712 were treated with olmesartan at an average dose of 27.2±12.6 mg (47.1% of patients taking the full drug dosage) and 714 treated with ramipril at an average dose of 7.3±3.1 mg (55.3% of patients taking the full drug dosage, \( P=0.008 \) vs olmesartan).

As shown in Table 1, no statistically significant differences existed between the two treatment groups for the main demographic and clinical characteristics at baseline.
Table 1 Demographic and clinical characteristics of the 1,426 patients of the intention-to-treat population of the two studies pooled together

<table>
<thead>
<tr>
<th></th>
<th>Olmesartan 10–40 mg (n=712)</th>
<th>Ramipril 2.5–10 mg (n=714)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.0±5.2</td>
<td>72.1±5.0</td>
<td>0.689</td>
</tr>
<tr>
<td>65–69</td>
<td>298 (41.9)</td>
<td>299 (41.9)</td>
<td>0.954</td>
</tr>
<tr>
<td>70–79</td>
<td>351 (49.3)</td>
<td>355 (49.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>63 (8.8)</td>
<td>60 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>355 (49.9)</td>
<td>362 (50.7)</td>
<td>0.751</td>
</tr>
<tr>
<td>Female</td>
<td>357 (50.1)</td>
<td>352 (49.3)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.8±8.7</td>
<td>165.5±8.7</td>
<td>0.623</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.8±11.8</td>
<td>74.1±11.5</td>
<td>0.613</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8±3.5</td>
<td>27.0±3.2</td>
<td>0.339</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.1±11.6</td>
<td>96.3±11.5</td>
<td>0.790</td>
</tr>
<tr>
<td>Significant medical history</td>
<td>586 (82.3)</td>
<td>588 (82.4)</td>
<td>0.980</td>
</tr>
<tr>
<td>Concomitant treatments</td>
<td>480 (67.4)</td>
<td>492 (68.9)</td>
<td>0.545</td>
</tr>
<tr>
<td>Hypertension medication in the previous 3 months</td>
<td>538 (75.6)</td>
<td>537 (75.2)</td>
<td>0.877</td>
</tr>
<tr>
<td>Number of previous antihypertensive drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>174 (24.4)</td>
<td>179 (25.1)</td>
<td>0.682</td>
</tr>
<tr>
<td>1</td>
<td>348 (48.9)</td>
<td>333 (46.6)</td>
<td></td>
</tr>
<tr>
<td>2 or more</td>
<td>190 (26.7)</td>
<td>202 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Type of previous antihypertensive drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>208 (38.7)</td>
<td>214 (39.9)</td>
<td>0.672</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>215 (40.0)</td>
<td>210 (39.2)</td>
<td>0.793</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>170 (31.6)</td>
<td>127 (23.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diuretics</td>
<td>54 (10.0)</td>
<td>73 (13.6)</td>
<td>0.069</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>85 (15.8)</td>
<td>100 (18.7)</td>
<td>0.215</td>
</tr>
<tr>
<td>Alpha-blockers</td>
<td>36 (6.7)</td>
<td>43 (8.0)</td>
<td>0.403</td>
</tr>
<tr>
<td>Others</td>
<td>10 (1.9)</td>
<td>12 (2.2)</td>
<td>0.660</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>372 (52.2)</td>
<td>363 (50.8)</td>
<td>0.595</td>
</tr>
<tr>
<td>Central or peripheral obesity</td>
<td>557 (78.2)</td>
<td>573 (80.3)</td>
<td>0.347</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>601 (84.4)</td>
<td>610 (85.4)</td>
<td>0.589</td>
</tr>
<tr>
<td>Diabetes</td>
<td>138 (19.4)</td>
<td>153 (21.4)</td>
<td>0.338</td>
</tr>
<tr>
<td>CKD stages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal or increased eGFR (≥90 mL/min/1.73 m²)</td>
<td>89 (12.5)</td>
<td>92 (12.9)</td>
<td>0.973</td>
</tr>
<tr>
<td>Slightly reduced eGFR (60–90 mL/min/1.73 m²)</td>
<td>421 (59.1)</td>
<td>419 (58.7)</td>
<td></td>
</tr>
<tr>
<td>Moderately or severely reduced eGFR (&lt;60 mL/min/1.73 m²)</td>
<td>202 (28.4)</td>
<td>203 (28.4)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular risk level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-moderate (≤5%)</td>
<td>80 (11.2)</td>
<td>79 (11.1)</td>
<td>0.918</td>
</tr>
<tr>
<td>High-very high (&gt;5%)</td>
<td>632 (88.8)</td>
<td>635 (88.9)</td>
<td></td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>157.1±10.0</td>
<td>156.6±10.0</td>
<td>0.407</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>91.8±6.7</td>
<td>91.3±6.7</td>
<td>0.103</td>
</tr>
<tr>
<td>Type of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic ± systolic</td>
<td>550 (77.2)</td>
<td>527 (73.8)</td>
<td>0.131</td>
</tr>
<tr>
<td>Isolated systolic</td>
<td>162 (22.8)</td>
<td>187 (26.2)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Data are shown as means (± SD) or as absolute (n) and relative (%) frequencies. P-values for between-treatment difference are also reported. *Available for 699 patients randomized to olmesartan and for 703 patients randomized to ramipril. †Percentages refer to treated patients (n=1,074).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; ACE, angiotensin-converting enzyme.

As expected, using the new cutoffs, the rate of normalization at 12 weeks (study end) increased as compared to the original reports, being still significantly larger under olmesartan than under ramipril (Figure 1). When the blood pressure target was set at ≤140/90 mmHg for all patients, 55.2% of olmesartan-treated patients attained blood pressure normalization vs 48.6% of ramipril-treated patients (P=0.013). The use of a less rigid target (<150/90 mmHg), as indicated for the elderly, resulted in 70.1% rate of normalization under olmesartan and 63.2% under ramipril (P=0.006) at the end of the study. The superiority of olmesartan was observed at each study time point and the difference vs ramipril was statistically significant, except in one case.
A summary of other studies assessing the efficacy of olmesartan monotherapy in elderly hypertensive patients is reported in Table 2. Although the studies performed so far are not entirely homogenous for design, inclusion criteria, study duration, and endpoints, some similarities with our results may be observed, at least for some studies. For instance, the application of new blood pressure targets to our data gave results superimposable to those observed in a similar study by Kereiakes et al which made use of olmesartan at dosages of 20 or 40 mg with blood pressure targets evaluated at $<140/90$ mmHg (Table 2). Our responder rate was also not dissimilar from that observed in a study by Saito et al employing olmesartan monotherapy at dosages of 5–40 mg, with the addition of other antihypertensive drugs. In the other three

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**Figure 1** Percentage of normalized patients according to different thresholds.

**Notes:** (A) Original study thresholds, $<140/90$ mmHg in nondiabetics and $<130/80$ mmHg in diabetics. (B) $<140/90$ mmHg for all patients. (C) $<150/90$ mmHg for all patients after 2, 6, and 12 weeks of treatment with olmesartan 10–40 mg (white bars) or ramipril 2.5–10 mg (black bars). $P$-values for between-treatment difference are also reported.
Table 2 Blood pressure response to olmesartan monotherapy in elderly patients with systolic and/or diastolic hypertension or isolated systolic hypertension in different open-label or double-blind randomized studies

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Country</th>
<th>Number of patients</th>
<th>Study design</th>
<th>Age (years)</th>
<th>BP at entry</th>
<th>Washout (weeks)</th>
<th>Treatment duration</th>
<th>Type of treatment</th>
<th>Blood pressure normalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kereiakes et al 2009</td>
<td>USA</td>
<td>176</td>
<td>Open-label, randomized, blinded endpoint</td>
<td>≥65</td>
<td>DBP ≥90 mmHg and/or SBP ≥140 mmHg</td>
<td>2 (placebo)</td>
<td>12 weeks</td>
<td>Olmesartan 20 or 40 mg</td>
<td>BP &lt;140/90 mmHg: 52.3%</td>
</tr>
<tr>
<td>Saito et al 2008</td>
<td>Japan</td>
<td>481</td>
<td>Open-label, randomized, prospective</td>
<td>≥65</td>
<td>DBP ≥90 mmHg and/or SBP ≥140 mmHg</td>
<td>None</td>
<td>24 weeks</td>
<td>Olmesartan 5, 10, 20 or 40 mg (+ other antihypertensive drugs)</td>
<td>BP &lt;140/90 mmHg: 50.0%</td>
</tr>
<tr>
<td>Heagerty and Mallion 2009</td>
<td>Europe</td>
<td>251</td>
<td>Double-blind, randomized</td>
<td>≥65</td>
<td>DBP 100–114 mmHg</td>
<td>2 (placebo)</td>
<td>52 weeks</td>
<td>Olmesartan 20 or 40 mg</td>
<td>BP &lt;140/90 mmHg: 74.5%</td>
</tr>
<tr>
<td>Ogawa et al 2012</td>
<td>Japan</td>
<td>578</td>
<td>Open-label, randomized, prospective, blinded endpoint</td>
<td>65–84</td>
<td>DBP ≥90 mmHg and/or SBP ≥140 mmHg</td>
<td>2–4 (olmesartan 20 mg)</td>
<td>3 years</td>
<td>Olmesartan 40 mg</td>
<td>BP &lt;140/90 mmHg: 62.1%</td>
</tr>
<tr>
<td>Mallion et al 2007</td>
<td>Europe</td>
<td>256</td>
<td>Double-blind, randomized</td>
<td>≥65</td>
<td>DBP &lt;90 mmHg and/or SBP 161–200 mmHg</td>
<td>2 (placebo)</td>
<td>24 weeks</td>
<td>Olmesartan 20 or 40 mg</td>
<td>SBP ≤135 mmHg: 67.6%</td>
</tr>
</tbody>
</table>

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; BP, blood pressure.
risk of cardiovascular events. This is particularly relevant because there is consistent evidence that olmesartan may reduce cardiovascular risk by simultaneously normalizing blood pressure and reversing the proatherogenic effects of angiotensin II, an effect which is particularly desirable in the elderly.\(^{30,31}\)

### Blood pressure response according to type of hypertension

Olmesartan medoxomil also proved to be effective in controlling blood pressure, regardless of the type of hypertension. Most of the studied patients (75.5\%) were affected by diastolic ± systolic hypertension. In these patients, the chance of attaining blood pressure normalization was significantly larger under olmesartan than under ramipril for both the thresholds considered (<140/90 mmHg: 54.4\% vs 46.7\%, P=0.012; <150/90 mmHg: 68.4\% vs 60.3\%, P=0.006), confirming the results of the original analysis. In three previous studies, which enrolled a total of 1,235 hypertensive patients aged ≥65 years, the proportion of patients with a blood pressure <140/90 mmHg at the end of the study who were given olmesartan at doses 5–40 mg was 56.0\%, thus very close to our finding.\(^{21,22,24}\)

In our population, isolated systolic hypertension was less common than diastolic ± systolic hypertension (24.5\%), but the chance of achieving blood pressure normalization with treatment was similar for the two hypertension subtypes. As in the original publication, no statistically significant differences were observed between the treatment groups in terms of blood pressure normalization either considering the 140/90 mmHg (olmesartan 58.0\% vs ramipril 54.0\%, P=0.451) or the 150/90 mmHg cutoff (75.9\% vs 71.1\%, P=0.311). Such results indicate that also in a relatively small subgroup of high-risk patients such as those with isolated systolic hypertension, olmesartan is capable of adequately controlling blood pressure.

### Blood pressure response in patients with metabolic disorders

The metabolic syndrome is characterized by the association of different cardiovascular risk factors such as abdominal obesity, atherogenic dyslipidemia, insulin resistance or glucose intolerance, and blood pressure elevation.\(^{32}\) Patients suffering from this condition have a higher risk of cardiovascular fatal and nonfatal events than healthy people, particularly in the presence of diabetes mellitus.\(^{33,34}\) Treatment with a drug acting on the renin–angiotensin system (RAS) has been shown to be particularly effective for controlling blood pressure and reducing major cardiovascular events, in the presence of metabolic abnormalities, such as metabolic syndrome or diabetes.\(^{35-37}\)

In the pooled analysis of our studies, we analyzed the antihypertensive effect of olmesartan and ramipril in patients with metabolic syndromes, defined according to the International Diabetes Federation criteria and observed a significantly higher proportion of normalized patients under olmesartan, irrespective of the blood pressure target considered (Figure 2).\(^{38,39}\) In addition to this finding, we observed a superior efficacy of olmesartan vs ramipril in patients with central or peripheral obesity (waist circumference >102 cm in men and >88 cm in women, or body mass index ≥30 kg/m\(^2\)), as well as in those with dyslipidemia (total cholesterol >190 mg/dL, or low-density lipoprotein cholesterol >115 mg/dL, or high-density lipoprotein cholesterol <40 mg/dL in men and <46 mg/dL in women, or triglycerides >150 mg/dL, or under specific treatment...
with a lipid lowering drug). The superiority of olmesartan for controlling blood pressure in patients with metabolic disorders may be explained by an overexpression of vascular angiotensin II type 1 (AT1) receptors and overactivation of the RAS, which are the targets for the drug, and by a more specific inhibiting action of the ARB on the systemic and adipose tissue RAS.

Despite a high rate of blood pressure normalization in the subgroup of diabetics, no statistically significant differences were observed between the two treatment groups (Figure 2). The fact that olmesartan is as effective as ramipril in diabetic patients is in line with the results of a recent meta-analysis of 23 randomized controlled studies comparing ARBs and ACE-inhibitors: no significant difference was found in the proportion of patients who achieved successful blood pressure control on a single antihypertensive agent of the ARB or ACE-inhibitor class.

**Blood pressure goal attainment according to renal function status**

An impaired renal function is a frequent finding in hypertensive patients and constitutes a very potent predictor of future cardiovascular events. Current evidence supports the use of ARBs or ACE inhibitors as the therapy of choice for hypertension in patients with chronic kidney disease, due to specific renoprotective effects of these drugs, which are beyond their antihypertensive effect.

A post hoc analysis of the two pooled studies has previously shown that olmesartan medoxomil is efficacious in controlling blood pressure in the elderly patients of the

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**Figure 2** Percentage of normalized patients.  
Notes: (A) \(<140/90\) mmHg, (B) \(<150/90\) mmHg after 12 weeks of treatment with olmesartan 10–40 mg (white bars) or ramipril 2.5–10 mg (black bars) according to the presence of specific metabolic abnormalities. \(p\)-values for between-treatment difference are also reported.
study, independently of their renal function status, assessed
by estimated glomerular filtration rate (eGFR), using the
Cockcroft–Gault equation. The efficacy of olmesartan proved
to be generally superior to that of ramipril, in terms of blood
pressure normalization, particularly in patients with normal
or increased eGFR (≥90 mL/min/1.73 m²) and in those
with slightly reduced eGFR (60–90 mL/min/1.73 m²). Data
reanalysis based on the currently recommended blood pressure
targets (<140/90 or <150/90 mmHg) confirmed a statistically
significant superiority of olmesartan vs ramipril in the normal
or increased eGFR subgroup, with a comparable efficacy of
the two drugs in the other two categories (Figure 3).

Thus, it seems that RAS inhibition is effective in con-
trolling blood pressure in older hypertensives, regardless of
the renal status of the patients, even when less tight blood
pressure control is required. Also in this case, as in the case
of a tighter blood pressure control, olmesartan may help
achieving a better blood pressure control in the subgroup of
patients with a preserved renal function or at an early stage
of the kidney disease.

Patients at target according to number and types of previous antihypertensive
treatment

Patients with hypertension at highest risk of cardiovascular
complications, such as older persons, have a greater chance
of being resistant to particular classes of drugs or may
not adequately respond to monotherapy. In order to gain

Figure 3 Percentage of normalized patients.
Notes: (A) <140/90 mmHg, (B) <150/90 mmHg after 12 weeks of treatment with olmesartan 10–40 mg (open square) or ramipril 2.5–10 mg (full square) according to estimated glomerular filtration rate (eGFR). P-values for between-treatment difference are also reported.
further insight into the mechanisms behind the efficacy of olmesartan and ramipril in our pooled datasets of aged hypertensives, we evaluated response rate in subgroups of patients according to the number of drugs and type or RAS antagonist (ARB or ACE inhibitor) used at the time of entering the studies.

In never-treated patients (24.8% of the whole study population), olmesartan ability to achieve the blood pressure target, whether it was based on the 140/90 or the 150/90 mmHg threshold, was better than that of ramipril (with statistically significant differences for the <140/90 mmHg target), suggesting that the subgroup of patients of our population previously receiving no antihypertensive drug was more prone to respond to the ARB than to the ACE inhibitor (Figure 4). Additionally, olmesartan appeared to be significantly superior to ramipril in the subgroup of patients that were previously treated with a combination therapy, suggesting that an olmesartan-based monotherapy may be a possible choice for patients that are less susceptible to an adequate blood pressure response to previous multiple antihypertensive treatment.

Blood pressure response to a RAS inhibitor may be reduced or event blunted in patients previously not responding to a drug from the same class. In our population, the rate of blood pressure control was similar with olmesartan and ramipril, independently of the kind of previous antihypertensive treatment, whether it was based on an ACE inhibitor or an ARB (Figure 4).

Figure 4 Percentage of normalized patients.
Notes: (A) <140/90 mmHg, (B) <150/90 mmHg after 12 weeks of treatment with olmesartan 10–40 mg (white bars) or ramipril 2.5–10 mg (black bars) according to the number and type of previous antihypertensive drugs. P-values for between-treatment difference are also reported.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.
Drug safety according to blood pressure targets

As previously shown, 44 patients (3.1%) reported 67 adverse events attributed to study treatment: 21 patients received olmesartan (33 adverse events) and 23 ramipril (34 adverse events) (P=0.767 between treatments). The rate of patients with drug-related adverse events was the same in the group normalized at a target of <140/90 mmHg (23 of 740 patients, 3.1%) and of <150/90 mmHg (20 of 950 patients, 3.1%, P=0.948). In these two target groups, the rate of patients reporting adverse events attributed to study drug never differed between treatments (<140/90 mmHg: olmesartan 2.0% vs ramipril 4.3%, P=0.074; <150/90 mmHg: olmesartan 2.2% vs ramipril 4.0%, P=0.110). Thus, in our study, the risk of reporting an adverse drug reaction was not related to the blood pressure level achieved during treatment.

Discussion and overall conclusion

All current hypertension guidelines have raised the target blood pressure goals in older hypertensive patients, while eliminating the tighter control recommendations in patients with diabetes and renal disease. Notwithstanding such recommendations, strong debate exists among scientists on whether, in older or high-risk populations, blood pressure cutoffs should remain more conservative, namely kept higher, or rather a more aggressive approach should be followed, as it was in the past. The disagreement between studies and the difficulty in weighting the available evidence in the absence of definite data are reflected in the guidelines: some of them recommend a blood pressure target of <150/90 mmHg for persons older than 60 years, whereas others recommend a goal of <140/90 mmHg, in persons aged 80 years or younger and <150/90 mmHg only in frail persons aged 80 years or more.

We attempted to provide a better insight into this controversy, by reanalyzing the results of two large randomized studies at the light of the new blood pressure targets recommended by present hypertension guidelines. As in the original study, the efficacy of olmesartan was not negatively affected by age, sex, hypertension type, diabetes status, or other concomitant clinical conditions or cardiovascular risk factors. In most cases, olmesartan provided better blood pressure control than ramipril. Olmesartan was significantly more effective than ramipril in male patients, in younger patients (aged 65–59 years), in patients with a normal eGFR, and in those with diastolic ± systolic hypertension. Olmesartan showed better results than ramipril also in specific categories of high-risk patients, such as those with metabolic syndrome, obesity, dyslipidemia, and in general, in patients with a high or very high cardiovascular risk. Interestingly, patients previously untreated or treated with two or more antihypertensive drugs showed a significantly larger response with olmesartan than with ramipril.

Having said so, we must acknowledge some limitations of our post hoc analysis. First, although we pooled together data from two adequately powered, randomized, double-blind, parallel group studies with an identical design, the fact of raising the target of adequate blood pressure control and applying less stringent criteria increased per se the rate of responders in both study treatments. This is because in the original study drug, up titration and treatment tailoring were based on targets lower than those used in this reanalysis (<140/90 mmHg in nondiabetic patients and <130/80 mmHg in diabetic patients). Second, we should acknowledge as a potential source of difference among treatment groups the fact that the antihypertensive effect of the maximum dose of ramipril employed in our study (10 mg) might not correspond in terms of efficacy to that of olmesartan (40 mg). The use of higher doses of ramipril could have allowed achieving better responses, but in the original study, comparisons were limited to the maximum doses currently recommended for the two drugs. Third, one meta-analysis documented that while the blood pressure dependent effects of ACE inhibitors and ARBs on the risk of stroke, coronary heart disease, and heart failure are similar, ACE inhibitors but not ARBs have blood pressure independent effect on the risk of major coronary disease events. Very recently, a systematic review showed that ACE inhibitors are more effective in preventing coronary heart disease and less in preventing stroke, whereas ARBs are inferior in preventing coronary heart disease. However, the blood pressure lowering effect of the two classes of drugs in hypertensive patients seems to be quite superimposable.

Thus, in spite of some superiority in terms of antihypertensive effect of a given ARB over a given ACE inhibitor, as in our study, we must admit that there is no evidence in medical literature to recommend ARB over ACE inhibitor therapy. Differences found among active principles may instead suggest specific choices in specific conditions, or preferable combinations of drugs and doses. Fourth, in our study we showed a better blood pressure response with olmesartan, but we could not demonstrate any superiority in terms of prevention of cardiovascular outcomes because these endpoints were not assessed in the study. Thus, we cannot conclude that olmesartan is superior to ramipril in terms of cardiovascular protection in the elderly hypertensive patient.
Notwithstanding these limitations, our results may be relevant for the clinical practice, providing some indication on the possible different response of elderly hypertensive patients to two different RAS inhibitors, when patients are targeted according to the blood pressure levels recommended by recent hypertension guidelines.

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Author contributions
All authors contributed toward data analysis, drafting and critically revising the paper, and agree to be accountable for all aspects of the work.

Disclosure
SO, EM, JMM, and MV have occasionally received grants for lectures by the manufacturers of olmesartan or ramipril. MV has been consultant in scientific advisory board of Daiichi Sankyo, manufacturer of olmesartan.

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